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EDITORIAL COMMENT

Very Late Thrombosis After Bioresorbable Scaffolds

Cause for Concern?*

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The absence of clinical restenosis in the first major trial of metallic drug-eluting stents (DES) (1) elicited unbridled enthusiasm among interventional cardiologists. However, it did not take long to realize that, although DES were a marked improvement over bare-metal stents (2), they were not perfect. Specifically, McFadden and et al. (3) reported a new complication in 4 patients, late stent thrombosis occurring after discontinuation of dual antiplatelet therapy (DAPT) (3). Since then, we have learned that target lesion-related failures after 1 year (including restenosis as well as thrombosis) occur at a frequency of 2% to 3% per year for all permanent metallic stents, a rate that may continue for 20 years or longer (4,5). The mechanisms contributing to these stent-related failures are multifactorial and include incomplete endothelialization, persistent inflammation, vessel straightening and compliance mismatch, strut fracture, neoatherosclerosis, and others. Bioresorbable vascular scaffolds (BVS), which provide the mechanical support and drug elution capability of metallic DES for the first 12 months post-implantation and then completely resorb over several years, were developed to improve long-term outcomes after coronary intervention.

The presentation in this issue of the *Journal* of 4 cases of very late scaffold thrombosis (VLScT), occurring >1 year after implantation of the Absorb BVS (Abbott Vascular, Santa Clara, California) (6), may thus raise eyebrows if not outright concerns of "déjà vu." The greatest incremental effects of BVS on improving very late outcomes, however, are likely to be shown after their complete resorption, which occurs in ~3 years for the poly(L-lactide) (PLLA) Absorb scaffold in healthy porcine coronary arteries (7). Three of the 4 cases reported by Räber et al. (6) occurred before that time period, so perhaps the outcomes are not too surprising. The fourth case at 44 months demonstrates that BVS will not eliminate very late adverse events. What additional insights may be gleaned from these 4 cases?

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First, optical coherence tomography (OCT) showed uncovered struts apposed to the vessel wall were detected in all cases (range: 2.6% to 8.0%) and were associated with adherent thrombus. Although a causal relationship between uncovered stent struts and very late thrombosis after metallic DES has never been demonstrated, incomplete endothelialization at the treated lesion site due to drug and/or persistent polymer effects may underlie some cases of very late thrombosis after both metallic DES and polymeric BVS.

Second, the apparent detection of PLLA-like material at 44 months raises questions concerning the time course and variability of Absorb scaffold resorption in humans and its potential role in VLScT. In porcine models, PLLA levels in coronary artery tissue measured using gel permeation high-pressure liquid chromatography fall below the limit of quantification (<3% of the original weight) within 3 years (7).

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Similarly, intravascular ultrasound-based vessel wall echogenicity progressively declines over this period, along with the scaffold's molecular weight (8). OCT-defined "preserved boxes" at 3 years are rarely seen in this model, correlating with histological evidence of polymer resorption (9). Thus, whereas the presence of preserved boxes in the 3 reported VLScT cases occurring within 24 months is not surprising, their persistence in the case that thrombosed at 44 months might not have been expected. Is the PLLA resorption rate the same in humans as in swine, and do the preserved boxes still contain PLLA, as opposed to cellular or connective tissue? Although it is difficult to address these questions directly in humans, polymer degradation is driven by a hydrothermal process (i.e., dependent on water concentration and temperature) and is independent of other cellular and enzymatic processes occurring outside the polymer boundaries. It is possible that extracellular matrix and cellular components may fill the voids left behind following PLLA resorption, leading to a similar preserved box configuration on OCT. In the present report, the presence of PLLA-like material in Fourier transform infrared spectroscopy (FTIR) at 44 months in a single case is suggestive but not definitive evidence of its presence, as other biological materials and catheter components may share a similar FTIR fingerprint. However, the fact that small zones of birefringence were evident in the thrombus aspirate makes it probable that PLLA-like material was present, perhaps in a protected crystalline form with somewhat delayed temporal absorption. However, the amount of PLLA recovered was very small, likely below the level of quantification by current analytical techniques, and is unlikely to have contributed to the VLScT event.

Third, cases 1, 2, and 4 of the present report suggest a novel mechanism of VLScT not seen with metallic DES, that of intraluminal scaffold dismantling (ILSD). Natural dismantling of the scaffold architecture by bulk erosion, first with interruption of the hoops between the scaffold rings occurring as early as 6 months, is integral to the benefits seen with BVS. This process allows return of cyclic pulsatility and vasomotion, restoration of native vessel curvature, and expansive remodeling (7). Serial OCT imaging has demonstrated that late scaffold discontinuities are common but rarely associated with clinical adverse events (10). Such natural "fractures," if mechanically restrained by neointimal tissue, do not abut into the lumen and are of no clinical consequence. Conversely, scaffold dismantling with macroscopic space-occupying structures protruding into the lumen (such as with ILSD) may occur either at the time of implantation (excessive polymer stretching or elongation at break [usually by use of a balloon ≥0.75 mm larger than the nominal diameter in the case of Absorb]), or at any time due to excessive biomechanical cyclic stress (high bending forces) or iatrogenic causes (disruption by interventional catheters of an already friable device undergoing biodegradation), in cases without a well-formed neointima. Thus, although it is conceivable that ILSD may have contributed to VLScT in the present report, it is also possible that passage of OCT and thrombus aspiration catheters may have caused scaffold disruption. The implications of this phenomenon are that caution is warranted when passing devices through the BVS within several years after implantation (immediately withdrawing the catheter if resistance is felt) and that prolonged DAPT, if ILSD is visualized, be considered, at least in patients at low risk for bleeding. Re-stenting with a metallic DES may also be appropriate in severe cases of ILSD.

Fourth and finally, small lumen scaffold areas were evident in all 4 VLScT cases, which suggests either suboptimal scaffold expansion at the time of implantation or structural biomechanical failure occurring during the process of scaffold resorption (e.g., ILSD). Lack of serial imaging in these patients limits our ability to further ascertain the mechanism of these observations. However, the BVS visually appear under-expanded in all 4 cases, as confirmed by the residual angiographic diameter stenosis ranging from 18.6% to 26.7%. Careful lesion preparation (pre-dilation) and optimal scaffold expansion (post-dilation with noncompliant balloons at high pressure) are required to maximize lumen gain with first-generation BVS. A small minimal stent area is the most important determinant of late thrombosis, at least for metallic stents (11) and would be expected to be even more important for thicker strut first-generation BVS. Conversely, acute strut malapposition has never been shown to be related to metallic stent thrombosis, as long as the stent area is sufficient (11). Further studies are required to determine whether this holds for BVS as well.

In conclusion, the clinical report by Räber et al. (6), although only a retrospective collection of a small number of cases, provides useful insight into the possible causes of very late device failures among patients receiving first-generation BVS technology. Some of these mechanisms appear to be similar to those for metallic DES. However, the present report also suggests that ILSD may be a novel cause of very late BVS thrombosis. Conversely, longitudinal stent deformation and late strut fractures of metallic DES are occasional causes of very late stent thrombosis that BVS may reduce (12,13). There are also many

unknowns. For example, given continuous exposure to lipid and cellular trafficking throughout the resorption process, will neoatherosclerosis (an important cause of very late thrombosis after metallic DES) be less common with BVS (14)? Most importantly, the denominator of BVS implants without VLScT during the study period was not reported, and the fact that "only" 4 such cases have surfaced may alternatively be considered reassuring. Whether BVSs do indeed reduce very late thrombotic (and restenotic) events compared to metallic DES can only be addressed by large-scale, adequately powered randomized studies, such as the ongoing ABSORB IV trial (Absorb IV Randomized Controlled Trial [ABSORB IV]; NCT02173379). Moreover, BVS technologies will continue to evolve with the development of thinner strut platforms with enhanced biomechanical performance. Thus, at the present time we should not be "concerned" about VLScT after BVS—but we should be "aware!"

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